

REMARKS

1. Prior Art Issues (OA §11-16)

The Examiner has rejected claims 2-4 as anticipated by USP 5,961,979 based on evidence of Schiott et al. (1998) (OA §13).

The Examiner has also rejected claims 1-5, 21-51, 53 and 56 as anticipated by (OA §14) or obvious over (OA §16) over USP 5,874,085, based on evidence by Schiott et al. (1998) and, in the case of OA §15, UP 6,057,430.

These rejections are respectfully traversed.

1.1. Claim 1, as amended, is directed to a composition comprising a fragment consisting of SEQ ID NO:1, which is a subsequence of TGF-beta.

However, the Examiner has interpreted claim 1 as encompassing intact TGF-beta, based on a strained interpretation of "essentially consists of" (OA §12) and the scope of "functional equivalents" (allowing addition of amino acids). In our opinion, the overarching limitation "fragment" constrains the expansion of SEQ ID NO:1, by addition of amino acids, so it does not reach the point at which full-length TGF-beta is recreated. In any event, claim 1 as amended recites only "consisting" and does not recite "functional equivalents".

We realize that full-length TGF-beta "comprises" all possible "fragments" of TGF-beta, including SEQ ID NO:1. We wish to forestall any residual argument that a composition "comprising a fragment of TGF-beta" could read upon a composition comprising full-length TGF-beta. Applicant's intent was that the "fragment of claim 1(i) be interpreted as referring to an independent molecule, rather than as a sequence optionally linked to the remainder of TGF-beta. Thus, in Example 1, the composition comprised (1) a 29-amino acid polypeptide (TGF-29) corresponding to a fragment of TGF-beta and (2) a 17-amino acid polypeptide corresponding to a fragment of a Parvo Virus protein.

We have amended claim 1(i) to state that the composition comprises at least one peptide molecule, 29 amino acids in

length, corresponding to a fragment of TGF-beta.... We trust this will indisputably distinguish full-length TGF-beta.

1.2. The '979 rejection relies on the interpretation that the claims cover full-length TGF-beta. It is true that '085 teaches "fragments", but it does so generically, without reference to size or location. It does not teach that any particular fragment of TGF-beta is functional. This diffuse teaching cannot, as a matter of law, anticipate a claim specific to SEQ ID NO:1 (or a close group of equivalents). The '085 Examples only employed intact TGF-beta.

Turning to the new obviousness reference '430, its sequences ID4 and 10 are not immunostimulatory fragments. Rather, they are full length TGF betas (ID4 and 10 are 112 a.a., our ID 1 is 29 a.a.).

## 2. Enablement Issues (OA §7)

The Examiner concedes enablement for a composition comprising a fragment consisting of SEQ ID NO:1. The Examiner denied enablement for fragments comprising SEQ ID NO:1 or its "functional equivalents".

Claim 1, as amended, requires that the fragment be SEQ ID NO:1 or a mutant fragment differing from SEQ ID NO:1 by a single amino acid substitution.<sup>1</sup> Since SEQ ID NO:1 is 29 amino acids in length, that implies a sequence identity of greater than 95%. Basis for a single substitution exists at, e.g., P18, L11-12 and 31-33.

In support of the enablement rejection, the Examiner cites Ngo et al. Ngo et al. addresses the generic problem of predicting 3D structure from the amino acid sequence alone. He does not discuss the extent to which proteins retain activity after single amino acid substitutions, especially conservative substitutions as defined on page 11. And he does not specifically address TGF-beta.

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<sup>1</sup> Since amended claim 1 continues to read on SEQ ID NO:1, it still covers the elected species.

That said, we agree that even a single amino acid substitution can be detrimental to activity. However, the standard for enablement is one of undue experimentation. Since SEQ ID NO:1 is only 29 amino acids, it is within ordinary skill in the art to test all positions for tolerance of mutation by the standard technique known as alanine scanning mutagenesis (if Ala occurs natively, it can be replaced with Gly).

Moreover, the skilled worker will taken into account the known mammalian sequences of TGF- $\beta$ 1, - $\beta$ 2 and  $\beta$ 3 and which amino acids in their sequences are conserved. (P1, L18).

We must further point out that USP 5,061,786, as cited on page 5 of the office action, teaches specific amino acid substitutions.

Finally, we note that the Written Description Training Materials accept the combination of a 95% identity limitation with an activity limitation.

### 3. Description Issues (OA §8)

The Examiner also argues that the claims do not satisfy the 2001 revised interim guidelines re "written description". The issue is whether SEQ ID NO:1 is representative of the claimed genus. The amended genus falls within the "safe haven" set forth in the WDTM.

### 4. Definiteness Issues (OA §10)

4(A). The term "functional equivalents" is no longer used in the claims.

4(B). We believe that it would be clear to anyone skilled in the art that the meaning of "essentially consists of" is identical to that of "consists essentially of", a standard transitional phrase. (We therefore disagree with the interpretation adopted in OA §12). However, the issue is now moot.

4(C). We have amended claim 22 as suggested by the Examiner.

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4(D). We have cancelled 25 and made 26 dependent on 22.

5. Election/Restriction (OA §3)

5.1. The Examiner appears to assume that claims 6-20 are drawn to the unelected species (SEQ ID NO:1 mutant). That is incorrect. All of claims 6-20 still read on the elected species (SEQ ID NO:1). They merely say that if SEQ ID NO:1 is mutated, the mutation must take a particular form. Hence, claims 6-20 should be rejoined, and the next action on the merits, if it rejects any of claims 6-20, should not be made final, as claims 6-20 should have been examined in the December 17, 2004 action.

6. Foreign Priority (OA §5)

The priority document was filed on October 15, 2001. Enclosed herewith are copies of the request for priority, the first page of the certified copy, and our postcard receipt.

Respectfully submitted,

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